URSODIOL- ursosiol capsule
PD-Rx Pharmaceuticals, Inc.

Ursodiol Capsules, USP

Rx only

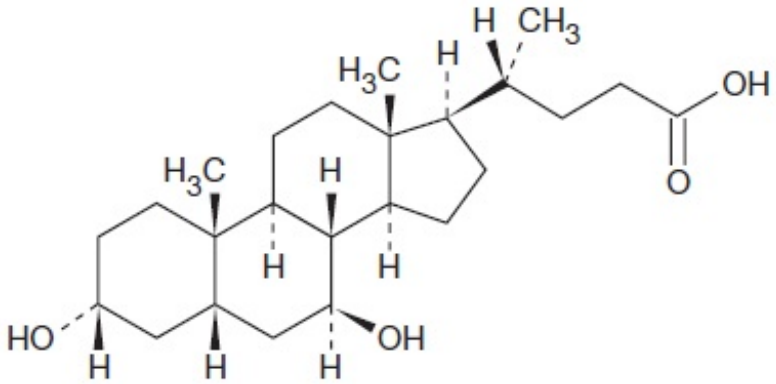
Prescribing Information

SPECIAL NOTE
Gallbladder stone dissolution with Ursodiol Capsules treatment requires months of therapy. Complete dissolution does not occur in all patients and recurrence of stones within 5 years has been observed in up to 50% of patients who do dissolve their stones on bile acid therapy. Patients should be carefully selected for therapy with ursodiol, and alternative therapies should be considered.

DESCRIPTION

Ursodiol Capsules, USP is a bile acid available as 300 mg capsules suitable for oral administration.

Ursodiol, USP is ursodeoxycholic acid, a naturally occurring bile acid found in small quantities in normal human bile and in the biles of certain other mammals. It is a bitter-tasting, white powder freely soluble in ethanol, methanol, and glacial acetic acid; sparingly soluble in chloroform; slightly soluble in ether; and insoluble in water. The chemical name for ursodiol is 3α,7β-Dihydroxy-5β-cholan-24-oic acid ($C_{24}H_{40}O_4$). Ursodiol, USP has a molecular weight of 392.57. Its structure is shown below:



*Inactive Ingredients:*Colloidal silicon dioxide, corn starch and magnesium stearate. Gelatin capsules contain red iron oxide, gelatin, and titanium dioxide. The capsules are printed with edible ink containing shellac, black iron oxide, propylene glycol, FD&C Blue # 2 aluminum lake, FD&C Red # 40 aluminum lake, D&C Yellow # 10 aluminum lake and FD&C Blue # 1 aluminum lake.

CLINICAL PHARMACOLOGY

About 90% of a therapeutic dose of ursodiol capsules is absorbed in the small bowel after oral administration. After absorption, ursodiol enters the portal vein and undergoes efficient extraction from portal blood by the liver (i.e., there is a large “first-pass” effect) where it is conjugated with either glycine or taurine and is then secreted into the hepatic bile ducts. Ursodiol in bile is concentrated in the gallbladder and expelled into the duodenum in gallbladder bile via the cystic and common ducts by gallbladder contractions provoked by physiologic responses to eating. Only small quantities of ursodiol appear in the systemic circulation and very small amounts are excreted into urine. The sites of the drug’s therapeutic actions are in the liver, bile, and gut lumen.

Beyond conjugation, ursodiol is not altered or catabolized appreciably by the liver or intestinal mucosa. A small proportion of orally administered drug undergoes bacterial degradation with each cycle of enterohepatic circulation. Ursodiol can be both oxidized and reduced at the 7-carbon, yielding either 7-keto-lithocholic acid or lithocholic acid, respectively. Further, there is some bacterially catalyzed deconjugation of glyco- and tauro-ursodeoxycholic acid in the small bowel. Free ursodiol, 7-keto-lithocholic acid, and lithocholic acid are relatively insoluble in aqueous media and larger proportions of these compounds are lost from the distal gut into the feces. Reabsorbed free ursodiol is reconjugated by the liver. Eighty percent of lithocholic acid formed in the small bowel is excreted in the feces, but the 20% that is absorbed is sulfated at the 3-hydroxyl group in the liver to relatively insoluble lithocholyl conjugates which are excreted into bile and lost in feces. Absorbed 7-keto-lithocholic acid is stereospecifically reduced in the liver to chenodiol.

Lithocholic acid causes cholestatic liver injury and can cause death from liver failure in certain species unable to form sulfate conjugates. Lithocholic acid is formed by 7-dehydroxylation of the dihydroxy bile acids (ursodiol and chenodiol) in the gut lumen. The 7-dehydroxylation reaction appears to be alpha-specific, i.e., chenodiol is more efficiently 7-dehydroxylated than ursodiol and, for equimolar doses of ursodiol and chenodiol, levels of lithocholic acid appearing in bile are lower with the former. Man has the capacity to sulfate lithocholic acid. Although liver injury has not been associated with ursodiol therapy, a reduced capacity to sulfate may exist in some individuals, but such a deficiency has not yet been clearly demonstrated.

Pharmacodynamics

Ursodiol suppresses hepatic synthesis and secretion of cholesterol, and also inhibits intestinal absorption of cholesterol. It appears to have little inhibitory effect on synthesis and secretion into bile of endogenous bile acids, and does not appear to affect secretion of phospholipids into bile.

With repeated dosing, bile ursodeoxycholic acid concentrations reach a steady-state in about 3 weeks. Although insoluble in aqueous media, cholesterol can be solubilized in at least two different ways in the presence of dihydroxy bile acids. In addition to solubilizing cholesterol in micelles, ursodiol acts by an apparently unique mechanism to cause dispersion of cholesterol as liquid crystals in aqueous media. Thus, even though administration of high doses (e.g., 15 - 18 mg/kg/day) does not result in a concentration of ursodiol higher than 60% of the total bile acid pool, ursodiol-rich bile effectively solubilizes cholesterol. The overall effect of ursodiol is to increase the concentration level at which saturation of cholesterol occurs.

The various actions of ursodiol combine to change the bile of patients with gallstones

from cholesterol-precipitating to cholesterol-solubilizing, thus resulting in bile conducive to cholesterol stone dissolution.

After ursodiol dosing is stopped, the concentration of the bile acid in bile falls exponentially, declining to about 5 to 10% of its steady-state level in about 1 week.

Clinical Results

Gallstone Dissolution

On the basis of clinical trial results in a total of 868 patients with radiolucent gallstones treated in 8 studies (three in the U.S. involving 282 patients, one in the U.K. involving 130 patients, and four in Italy involving 456 patients) for periods ranging from 6 to 78 months with ursodiol capsules doses ranging from about 5 - 20 mg/kg/day, an ursodiol capsules dose of about 8 - 10 mg/kg/day appeared to be the best dose. With an ursodiol capsules dose of about 10 mg/kg/day, complete stone dissolution can be anticipated in about 30% of unselected patients with uncalcified gallstones < 20 mm in maximal diameter treated for up to 2 years. Patients with calcified gallstones prior to treatment, or patients who develop stone calcification or gallbladder nonvisualization on treatment, and patients with stones > 20 mm in maximal diameter rarely dissolve their stones. The chance of gallstone dissolution is increased up to 50% in patients with floating or floatable stones (i.e., those with high cholesterol content), and is inversely related to stone size for those < 20 mm in maximal diameter. Complete dissolution was observed in 81% of patients with stones up to 5 mm in diameter. Age, sex, weight, degree of obesity, and serum cholesterol level are not related to the chance of stone dissolution with ursodiol capsules.

A nonvisualizing gallbladder by oral cholecystogram prior to the initiation of therapy is not a contraindication to ursodiol capsules therapy (the group of patients with nonvisualizing gallbladders in the ursodiol capsules studies had complete stone dissolution rates similar to the group of patients with visualizing gallbladders). However, gallbladder nonvisualization developing during ursodiol treatment predicts failure of complete stone dissolution and in such cases therapy should be discontinued.

Partial stone dissolution occurring within 6 months of beginning therapy with ursodiol capsules appears to be associated with a > 70% chance of eventual complete stone dissolution with further treatment; partial dissolution observed within 1 year of starting therapy indicates a 40% probability of complete dissolution.

Stone recurrence after dissolution with ursodiol capsules therapy was seen within 2 years in 8/27 (30%) of patients in the U.K. studies. Of 16 patients in the U.K. study whose stones had previously dissolved on chenodiol but later recurred, 11 had complete dissolution on ursodiol capsules. Stone recurrence has been observed in up to 50% of patients within 5 years of complete stone dissolution on ursodiol therapy. Serial ultrasonographic examinations should be obtained to monitor for recurrence of stones, bearing in mind that radiolucency of the stones should be established before another course of ursodiol capsules are instituted. A prophylactic dose of ursodiol capsules have not been established.

Gallstone Prevention

Two placebo-controlled, multicenter, double-blind, randomized, parallel group trials in a total of 1,316 obese patients were undertaken to evaluate ursodiol capsules in the prevention of gallstone formation in obese patients undergoing rapid weight loss. The

first trial consisted of 1,004 obese patients with a body mass index (BMI) ≥ 38 who underwent weight loss induced by means of a very low calorie diet for a period of 16 weeks. An intent-to-treat analysis of this trial showed that gallstone formation occurred in 23% of the placebo group, while those patients on 300, 600, or 1200 mg/day of ursodiol capsules experienced a 6%, 3%, and 2% incidence of gallstone formation, respectively. The mean weight loss for this 16-week trial was 47 lb for the placebo group, and 47, 48, and 50 lb for the 300, 600, and 1200 mg/day ursodiol capsules groups, respectively.

The second trial consisted of 312 obese patients (BMI ≥ 40) who underwent rapid weight loss through gastric bypass surgery. The trial drug treatment period was for 6 months following this surgery. Results of this trial showed that gallstone formation occurred in 23% of the placebo group, while those patients on 300, 600, or 1200 mg/day of Ursodiol capsuless experienced a 9%, 1%, and 5% incidence of gallstone formation, respectively. The mean weight loss for this 6-month trial was 64 lb for the placebo group, and 67, 74, and 72 lb for the 300, 600, and 1200 mg/day Ursodiol capsules groups, respectively.

ALTERNATIVE THERAPIES

Watchful Waiting

Watchful waiting has the advantage that no therapy may ever be required. For patients with silent or minimally symptomatic stones, the rate of development of moderate-to-severe symptoms or gallstone complications is estimated to be between 2% and 6% per year, leading to a cumulative rate of 7 to 27% in 5 years. Presumably the rate is higher for patients already having symptoms.

Cholecystectomy

For patients with symptomatic gallstones, surgery offers the advantage of immediate and permanent stone removal, but carries a high risk in some patients. About 5% of cholecystectomized patients have residual symptoms or retained common duct stones. The spectrum of surgical risk varies as a function of age and the presence of disease other than cholelithiasis.

Mortality Rates for Cholecystectomy in the U.S. (National Halothane Study, JAMA 1966; 197:775-8) 27,600 Cholecystectomies (Smoothed Rates) Deaths/1000 Operations***

	Age (Yrs)	Cholecystectomy	Cholecystectomy + Common Duct Exploration
Low Risk Patients*	0 - 49	.54	2.13
Women			
	50 - 69	2.80	10.10
Men	0 - 49	1.04	4.12
	50 - 69	5.41	19.23
High Risk Patients**	0 - 49	12.66	47.62
Women			
	50 - 69	17.24	58.82
Men	0 - 49	24.39	90.91

	50 - 69	33.33	111.11

* In good health or with moderate systemic disease.
** With severe or extreme systemic disease.
*** Includes both elective and emergency surgery.

Women in good health or who have only moderate systemic disease and are under 49 years of age have the lowest surgical mortality rate (0.054); men in all categories have a surgical mortality rate twice that of women. Common duct exploration quadruples the rates in all categories. The rates rise with each decade of life and increase tenfold or more in all categories with severe or extreme systemic disease.

INDICATIONS AND USAGE

1. Ursodiol Capsules are indicated for patients with radiolucent, noncalcified gallbladder stones < 20 mm in greatest diameter in whom elective cholecystectomy would be undertaken except for the presence of increased surgical risk due to systemic disease, advanced age, idiosyncratic reaction to general anesthesia, or for those patients who refuse surgery. Safety of use of ursodiol capsules beyond 24 months is not established.
2. Ursodiol capsules are indicated for the prevention of gallstone formation in obese patients experiencing rapid weight loss.

CONTRAINDICATIONS

1. Ursodiol capsules will not dissolve calcified cholesterol stones, radiopaque stones, or radiolucent bile pigment stones. Hence, patients with such stones are not candidates for ursodiol capsules therapy.
2. Patients with compelling reasons for cholecystectomy including unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis, or biliary-gastrointestinal fistula are not candidates for ursodiol capsules therapy.
3. Allergy to bile acids.

WARNINGS

Enteroliths in Patients with Risk for Intestinal Stenosis or Stasis

There have been rare postmarketing reports of ursodiol-treated patients who developed enteroliths (bezoars) resulting in obstructive symptoms that required surgical intervention. These patients had medical conditions that predisposed them to intestinal stenosis or stasis (e.g., surgical enteroanastomoses, Crohn's disease). If a patient presents with obstructive gastrointestinal symptoms, hold Ursodiol capsules until a clinical evaluation has been conducted.

PRECAUTIONS

Liver Tests

Ursodiol therapy has not been associated with liver damage. Lithocholic acid, a naturally occurring bile acid, is known to be a liver-toxic metabolite. This bile acid is formed in the

gut from ursodiol less efficiently and in smaller amounts than that seen from chenodiol. Lithocholic acid is detoxified in the liver by sulfation and, although man appears to be an efficient sulfater, it is possible that some patients may have a congenital or acquired deficiency in sulfation, thereby predisposing them to lithocholate-induced liver damage.

Abnormalities in liver enzymes have not been associated with ursodiol capsules therapy and, in fact, ursodiol capsules have been shown to decrease liver enzyme levels in liver disease. However, patients given ursodiol capsules should have SGOT (AST) and SGPT (ALT) measured at the initiation of therapy and thereafter as indicated by the particular clinical circumstances.

Drug Interactions

Bile acid sequestering agents such as cholestyramine and colestipol may interfere with the action of ursodiol capsules by reducing its absorption. Aluminum-based antacids have been shown to adsorb bile acids *in vitro* and may be expected to interfere with ursodiol capsules in the same manner as the bile acid sequestering agents. Estrogens, oral contraceptives, and clofibrate (and perhaps other lipid-lowering drugs) increase hepatic cholesterol secretion, and encourage cholesterol gallstone formation and hence may counteract the effectiveness of ursodiol capsules.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ursodeoxycholic acid was tested in 2-year oral carcinogenicity studies in CD-1 mice and Sprague-Dawley rats at daily doses of 50, 250, and 1000 mg/kg/day. It was not tumorigenic in mice. In the rat study, it produced statistically significant dose-related increased incidences of pheochromocytomas of adrenal medulla in males ($p = 0.014$, Peto trend test) and females ($p = 0.004$, Peto trend test). A 78-week rat study employing intrarectal instillation of lithocholic acid and tauro-deoxycholic acid, metabolites of ursodiol and chenodiol, has been conducted. These bile acids alone did not produce any tumors. A tumor-promoting effect of both metabolites was observed when they were co-administered with a carcinogenic agent. Results of epidemiologic studies suggest that bile acids might be involved in the pathogenesis of human colon cancer in patients who had undergone a cholecystectomy, but direct evidence is lacking. Ursodiol is not mutagenic in the Ames test. Dietary administration of lithocholic acid to chickens is reported to cause hepatic adenomatous hyperplasia.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits with ursodiol doses up to 200-fold the therapeutic dose and have revealed no evidence of impaired fertility or harm to the fetus at doses of 20- to 100-fold the human dose in rats and at 5-fold the human dose (highest dose tested) in rabbits. Studies employing 100- to 200-fold the human dose in rats have shown some reduction in fertility rate and litter size. There have been no adequate and well-controlled studies of the use of ursodiol in pregnant women, but inadvertent exposure of 4 women to therapeutic doses of the drug in the first trimester of pregnancy during the ursodiol capsules trials led to no evidence of effects on the fetus or newborn baby. Although it seems unlikely, the possibility that ursodiol can cause fetal harm cannot be ruled out; hence, the drug is not recommended for use during pregnancy.

Nursing Mothers

It is not known whether ursodiol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ursodiol capsules are administered to a nursing mother.

Pediatric Use

The safety and effectiveness of ursodiol capsules in pediatric patients have not been established.

Geriatric Use

In worldwide clinical studies of ursodiol capsules, approximately 14% of subjects were over 65 years of age (approximately 3% were over 75 years old). In a subgroup analysis of existing clinical trials, patients greater than 56 years of age did not exhibit statistically significantly different complete dissolution rates from the younger population. No age-related differences in safety and effectiveness were found. Other reported clinical experience has not identified differences in response in elderly and younger patients. However, small differences in efficacy and greater sensitivity of some elderly individuals taking ursodiol capsules cannot be ruled out. Therefore, it is recommended that dosing proceed with caution in this population.

ADVERSE REACTIONS

The nature and frequency of adverse experiences were similar across all groups.

The following tables provide comprehensive listings of the adverse experiences reported that occurred with a 5% incidence level:

GALLSTONE DISSOLUTION

	Ursodiol 8 - 10 mg/kg/day (N = 155)		**Placebo** (N = 159)	
	N	(%)	N	(%)
Body as a Whole				
Allergy	8	(5.2)	7	(4.4)
Chest Pain	5	(3.2)	10	(6.3)
Fatigue	7	(4.5)	8	(5.0)
Infection Viral	30	(19.4)	41	(25.8)
Digestive System				
Abdominal Pain	67	(43.2)	70	(44.0)
Cholecystitis	8	(5.2)	7	(4.4)
Constipation	15	(9.7)	14	(8.8)
Diarrhea	42	(27.1)	34	(21.4)
Dyspepsia	26	(16.8)	18	(11.3)
Flatulence	12	(7.7)	12	(7.5)
Gastrointestinal Disorder	6	(3.9)	8	(5.0)
Nausea	22	(14.2)	27	(17.0)
Vomiting	15	(9.7)	11	(6.9)
Musculoskeletal System				
Arthralgia	12	(7.7)	24	(15.1)

Arthritis	9	(5.8)	4	(2.5)
Back Pain	11	(7.1)	18	(11.3)
Myalgia	9	(5.8)	9	(5.7)
NervousSystem				
Headache	28	(18.1)	34	(21.4)
Insomnia	3	(1.9)	8	(5.0)
Respiratory System				
Bronchitis	10	(6.5)	6	(3.8)
Coughing	11	(7.1)	7	(4.4)
Pharyngitis	13	(8.4)	5	(3.1)
Rhinitis	8	(5.2)	11	(6.9)
Sinusitis	17	(11.0)	18	(11.3)
Upper Respiratory Tract Infection	24	(15.5)	21	(13.2)
Urogenital System				
Urinary Tract Infection	10	(6.5)	7	(4.4)

GALLSTONE PREVENTION

	Ursodiol 600 mg (N = 322)		**Placebo** (N = 325)	
	N	(%)	N	(%)
Body as a Whole				
Fatigue	25	(7.8)	33	(10.2)
Infection Viral	29	(9.0)	29	(8.9)
Influenza-like Symptoms	21	(6.5)	19	(5.8)
Digestive System				
Abdominal Pain	20	(6.2)	39	(12.0)
Constipation	85	(26.4)	72	(22.2)
Diarrhea	81	(25.2)	68	(20.9)
Flatulence	15	(4.7)	24	(7.4)
Nausea	56	(17.4)	43	(13.2)
Vomiting	44	(13.7)	44	(13.5)
Musculoskeletal System				
Back Pain	38	(11.8)	21	(6.5)
Musculoskeletal pain	19	(5.9)	15	(4.6)
NervousSystem				
Dizziness	53	(16.5)	42	(12.9)
Headache	80	(24.8)	78	(24.0)
Respiratory System				
Pharyngitis	10	(3.1)	19	(5.8)
Sinusitis	17	(5.3)	18	(5.5)
Upper Respiratory Tract Infection	40	(12.4)	35	(10.8)
Skin and Appendages				
Alopecia	17	(5.3)	8	(2.5)
Urogenital System				

Dysmenorrhea	18	(5.6)	19	(5.8)

Postmarketing Experience

The following adverse reactions, presented by system organ class in alphabetical order, have been identified during post-approval use of ursodiol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: enteroliths (bezoars)

OVERDOSAGE

Neither accidental nor intentional overdosing with ursodiol capsules have been reported. Doses of ursodiol capsules in the range of 16 - 20 mg/kg/day have been tolerated for 6 to 37 months without symptoms by 7 patients. The LD_{50} for ursodiol in rats is over 5000 mg/kg given over 7 to 10 days and over 7500 mg/kg for mice. The most likely manifestation of severe overdose with ursodiol capsules would probably be diarrhea, which should be treated symptomatically.

DOSAGE AND ADMINISTRATION

Gallstone Dissolution

The recommended dose for ursodiol capsules treatment of radiolucent gallbladder stones is 8 - 10 mg/kg/day given in 2 or 3 divided doses.

Ultrasound images of the gallbladder should be obtained at 6-month intervals for the first year of ursodiol capsules therapy to monitor gallstone response. If gallstones appear to have dissolved, ursodiol capsules therapy should be continued and dissolution confirmed on a repeat ultrasound examination within 1 to 3 months. Most patients who eventually achieve complete stone dissolution will show partial or complete dissolution at the first on-treatment reevaluation. If partial stone dissolution is not seen by 12 months of Ursodiol capsules therapy, the likelihood of success is greatly reduced.

Gallstone Prevention

The recommended dosage of ursodiol capsules for gallstone prevention in patients undergoing rapid weight loss is 600 mg/day (300 mg b.i.d.).

HOW SUPPLIED

Ursodiol Capsules, USP are pink opaque cap, white opaque body with black imprint “K237” on both cap and body containing white to off-white powder.

NDC 43063-871-60 Bottles of 60

NDC 43063-871-01 Bottles of 100

NDC 43063-871-93 Bottles of 180

Store at 20 to 25°C (68 to 77°F); excursions permitted within 15 ºto 30 ºC (59 ºto 86 ºF). [see USP Controlled Room Temperature].

Dispense in tight container (USP).

Keep out of reach of children.

For all medical inquiries contact:

KVK-Tech, Inc. Customer Service

1-215-579-1842

Package Label principal Display Panel

Ursodiol Capsules, USP

300 mg

Rx Only

URSODIOL

ursosiol capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43063-871(NDC:10702-237)

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
URSADIOL (UNII: 3D089V7L0K) (URSADIOL - UNII:3D089V7L0K)	URSADIOL	300 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

Product Characteristics

Color	pink (pink opaque) , white (white opaque)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	K237
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43063-871-60	60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	12/10/2019	
2	NDC:43063-871-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	07/26/2018	
3	NDC:43063-871-93	180 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	12/10/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210707	05/17/2018	

Labeler - PD-Rx Pharmaceuticals, Inc. (156893695)

Registrant - PD-Rx Pharmaceuticals, Inc. (156893695)

Establishment

Name	Address	ID/FEI	Business Operations
PD-Rx Pharmaceuticals, Inc.		156893695	repack(43063-871)

Revised: 7/2025 PD-Rx Pharmaceuticals, Inc.